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SUMMARY Two ataxia telangiectasia patients with unusual clinical and cellular features are described. Cultured fibroblasts and PHA stimulated lymphocytes from these two patients showed a smaller increase of radiosensitivity than cells from other A-T patients, as measured by colony forming ability or induced chromosome damage respectively, after exposure to ionising radiation. The response of DNA synthesis to irradiation of these cells was, however, the same as for other A-T patients. Cells from a third patient with some clinical features of A-T but with a very protracted course also showed low levels of radiation induced chromosome damage, but colony forming ability and the response of DNA synthesis after irradiation were no different from cells of normal subjects. There was, however, an increased level of translocations and unstable chromosomal rearrangements in this patient's lymphocytes.

Ataxia telangiectasia (A-T) is a recessively inherited disorder in which patients show a progressive cerebellar ataxia presenting in infancy or early childhood.[1] Other common neurological features include diminished or absent deep reflexes, flexor or equivocal plantar responses, choreoathetosis, oculomotor dyspraxia, and dysarthria.[1] Several of the other features may be variable in presentation or onset may be age dependent, for example, presence of bulbar telangiectasia and decreased levels of some serum immunoglobulins.[2] Consistent laboratory markers in these patients are an increased level of serum α fetoprotein,[3] a defect in cell mediated immunity,[4] an increased level of spontaneously occurring chromosomal rearrangements in peripheral blood lymphocytes,[5] and an unusual radiosensitivity of cultured cells.[5] There are some reports suggesting that different types of ataxia telangiectasia may be clinically recognisable.[6–10] Cox *et al*[9] also reported that different levels of cellular radiosensitivity may be observed between cell strains derived from different A-T patients, suggesting a degree of genetic heterogeneity. One A-T patient has also been described whose cultured lymphoblastoid cells showed a rate of DNA synthesis, after γ irradiation, no different from normal.[11] Chromosome translocations characteristic of A-T patients were found in his peripheral lymphocytes.[11] More direct evidence of genetic differences between patients has come from the demonstration of genetic complementation groups in A-T cell strains which apparently show the same degree of cellular radiosensitivity.[12 13]

Unusual cellular radiosensitivity has been reported in a further patient without clinical symptoms of ataxia telangiectasia, but who had a low level of serum IgA, growth retardation, microcephaly, facial erythema, and mental retardation.[14] Of some interest was the presence of spontaneously occurring chromosome translocations involving chromosomes 7 and 14 in the peripheral lymphocytes of this patient.[15 16] The relationship of this disorder to ataxia telangiectasia is unknown.

In the present study we describe two patients with clinically atypical ataxia telangiectasia whose cellular features can be distinguished from cells of other patients with this disorder. Cells from a third patient with a very protracted course are also described.

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Case reports

CASE 1

The patient is an eight year old female with one reportedly normal female sib. Her parents were

unrelated. Birth weight was 2835 g and there were no prenatal or perinatal problems. She is said to have walked on her own when about nine months old and no abnormality was noted in the attainment of her other milestones. After appearing to walk well she was believed to be knock-kneed and unsteady on her feet by three years of age and has become increasingly unsteady since.

She was a well built child with four café-au-lait patches and a fine capillary naevus and a small oval depigmented naevus on her right buttock. Her mother also had one depigmented area on the dorsum of the left hand but no other birth marks. The patient had choreoathetoid movements and showed diffuse cerebellar signs with depressed tendon reflexes. Bilateral conductive hearing loss compatible with a secretory otitis media was present. There was jerky nystagmus on horizontal gaze. Telangiectasia of the bulbar conjunctiva was minimal. Skull and chest *x* rays were normal. CT scanning suggested that the fourth ventricle was slightly larger than usual, but other than this there was no definite evidence of cerebellar disease. Nerve conduction studies showed no evidence of peripheral neuropathy. Blood count was normal. Serum immunoglobulin levels were IgA 1·7 g/l, IgG 8·5 g/l, and IgM 1·9 g/l. Alphafetoprotein levels were normal. This patient was designated AT1AB.

CASE 2

This patient is a 16 year old girl who has a gait disorder which appears to be due to a mixture of dystonia and ataxia, but she has a high degree of motor independence. Vertical eye movements are normal. There is slight to moderate dysarthria and drooling. Bulbar telangiectasia is minimal. Serum immunoglobulin levels were IgA 0·85 g/l, IgG 7·71 g/l, and IgM 2·04 g/l. Her serum α fetoprotein level was raised at 14·4 ng/ml. This patient was designated AT19BI.

CASE 3

This 45 year old female is the only child of unrelated Anglo-Indian and Anglo-Burmese parents. She was noted to be progressively unsteady from the age of first walking at 12 months. She became aware of clumsiness of the hands and slurring of speech in her early 20s, and her gait ataxia has slowly progressed to the extent that she can now only walk with support.

On examination she had a spastic dysarthria with inappropriate laughter and a supranuclear ophthalmoplegia. There was dystonic posturing of the upper limbs and mild limb ataxia. The ankle jerks were absent and the plantar responses extensor. Vibration sense was lost below the knees. There was a slight increase in conjunctival vascularity.

Serum IgA and IgG concentrations were normal but the IgM concentration was raised at 8·8 g/l. There was a moderate increase in serum α fetoprotein concentrations (22 ng/ml; normal up to 10). This patient was designated AT38BI.

Materials and methods

CELLS AND CULTURE CONDITIONS

Normal control fibroblast strains Con Bri, Con Cra, Con Bro, Con Bak, and Con SB, together with A-T fibroblast strains AT3BI, AT4BI, AT5BI, AT7BI, and AT8BI and the three variant fibroblast strains AT1AB, AT19BI, and AT38BI, were routinely grown in Dulbecco's modified Eagle's medium (DME) supplemented with 10% fetal calf serum (Flow Laboratories), glutamine, penicillin (100 IU/ml), and streptomycin (100 μg/ml) and incubated at 37°C in 5% CO_2 in air.

CHROMOSOME PREPARATIONS

For lymphocyte chromosome preparations, 0·4 ml of heparinised whole blood was cultured in 4·0 ml Ham's F10 medium supplemented with 10% bovine serum, 1% phytohaemagglutinin, penicillin, and streptomycin. The cultures were fixed at 48 or 72 hours. Lymphocytes were also *x* irradiated, either before culturing when they were in the G_0 stage of the cell cycle using a dose of 4·0 Gy and harvested at 48 hours, or four hours before harvesting at 48 hours (G_2 phase) of the cell cycle. A Pantak constant potential industrial radiography unit at 245 KV, 12 mA and half value thickness copper filter of 1 mm was used. The filter object distance was 30 cm and the dose rate 1·01 Gy per minute.

For trypsin banded chromosome preparations, 0·3 mg/ml thymidine was added for the last 16 hours of culture. Slide preparations of metaphases were incubated overnight at 60°C immersed in Hank's Balanced Salt Solution (1:1×10 HBSS/×1 HBSS) for 10 minutes, washed in pH 6·8 buffer, immersed in 2·8% trypsin in buffer for about 50 seconds, and rinsed in saline. Metaphases were stained with 20% Leishman's stain in pH 6·8 buffer for four minutes.

SURVIVAL CURVES

Different cell dilutions irradiated with doses of γ rays between 100 and 500 rads were seeded on to lethally irradiated feeder layers of the same cells (6×10^4 cells per 9 cm dish, irradiated with 35 Gy ^{60}Co γ rays). Cells were left for 14 to 21 days in an incubator to form colonies, with a change of medium once a week, and were then stained with methylene blue.

INHIBITION OF DNA SYNTHESIS

The response of DNA synthesis was investigated in

all A-T fibroblast strains and normal strains after exposure to γ irradiation. Cells were incubated for 24 hours at 37°C in growth medium containing 0·01 μCi/ml 2-^{14}C-thymidine (54 mCI/mmol). This medium was removed and replaced by Eagle's Minimal Essential Medium (MEM) (thymidine free) supplemented with 10% fetal calf serum and 10% glutamine (2 mmol/l for one hour). Cells were exposed to different doses of γ rays in situ on petri dishes. The medium was changed to fresh MEM and cells incubated for 30 minutes. DNA synthesis was measured by the addition of 10 μCi/ml methyl-^{3}H-thymidine (48 mCi/mmol) for 20 minutes at 37°C. This was removed and the cells washed in ice cold Dulbecco A buffer before adding 1 ml of 20% TCA and 200 μl EDTA (0·02%). The cells were scraped off the dishes using a rubber policeman and left for two hours to allow precipitation of the acid insoluble material. This was collected on Whatman GF/C filters and the filters washed three times in 5% trichloroacetic acid/2% sodium pyrophosphate. The filters were dissolved in Instagel and both ^{14}C and ^{3}H activity counted.

Measurement of the response of DNA synthesis to bleomycin treatment was undertaken in the same way using doses of up to 300 $\mu g/l^{-1}$ and exposure times of one hour.

Results

PRESENCE OF SPONTANEOUS CHROMOSOME ABNORMALITIES

After fixation at 48 hours, 100 lymphocyte metaphases from patient AT1AB stained with acetic orcein showed the presence of three apparent clone cells with a t(C;D) translocation (46, −D; −C; + small G like; + B like). No unstable rearrangement (dicentric or rings) or chromosome gaps or breaks were present in this sample (table 1). A 72 hour folic acid deficient culture showed one cell in 50 with a likely t(C;D) translocation. There was, however, no evidence of constitutional fragility, although one dicentric chromosome was also found in this sample. Of five Giemsa banded divisions, four were normal but the fifth had a balanced translocation between chromosomes 7 and 14 (46,XX,t(7;14)(q35;q12) (fig 1a). The level of sister chromatid exchanges was quite normal at 8·35±0·5.

In patient AT19BI, 50 trypsin banded metaphases were analysed and single cells with an inv(7)(p15q35), t(7;7)(p15;q35), t(14;14)(q11−12;q32), and t(6;15)(q23;q24) (fig 1b) were observed.

Patient AT38BI was distinguished by a low level

FIG 1 *(a) Translocation t(7;14)(q35;q12) present in about 3% of lymphocytes from AT1AB. (b) An unusual A-T translocation t(6;15)(q23;q24) observed in a single cell from patient AT19BI. (c) Translocation t(7;14)(q35;q12) in about 3% of lymphocytes from AT38BI.*

TABLE 1 *Chromosome analysis of lymphocytes from three variant A-T patients.*

Case	*Sex*	*Date of birth*	*No of cells analysed*	*Total normal*	*r*	*dic*	*f*	*ctg*	*ctb*	*csg*	*Clone cells*	*Cells with non-clonal rearrangements*	*Total abnormal cells*
AT1AB(1)	F	13.7.74	100	96	0	0	0	0	0	0	3	1	4
(2)*			50	47	0	1	1	0	1	0	1	0	3
AT19BI	F	12.11.69	50	46	0	0	0	0	0	0	0	4	4
AT38BI(1)	F	25.6.41	50	44	1	0	4	2	0	0	0	1	6
(2)			50	42	0	2	3	1	0	1	1†	2	8

*Second sample from AT1AB grown in folic acid deficient medium.
†t(7;14) translocation same as seen in sample (1). Two other t(7;14) translocations observed in 200 cells scanned for abnormalities of chromosome 7.
r=rings; dic=dicentric chromosomes; f=fragments; ctg=chromatid gaps; ctb=chromatid breaks; csg=chromosome gaps.

of stable rearrangements. Although only one cell with t(7;14)(q35;q11−12) was seen in the first blood sample, three further t(7;14)(q35;q11) translocations were observed in a second sample at a frequency of about 1% (fig 1c). This patient's lymphocytes also showed fragments and dicentrics (table 1).

LEVELS OF *X* RAY INDUCED CHROMOSOME ABNORMALITIES

Blood lymphocytes from patients AT5BI and AT19BI were irradiated simultaneously with normal controls at the G_2 stage of the cell cycle. Table 2 shows that after exposure to either 0·5 or 1·0 Gy, lymphocyte chromosomes from AT5BI were at least

TABLE 2 *Simultaneous irradiation of blood cultures, at G_2 or G_0, from normal and ataxia telangiectasia subjects.*

Patient	*Sample No*	*No of cells*	*r*	*dic*	*f*	*ctg*	*ctb*	*csg*	*tric*	*tri*	*qr*
After exposure to 0·5 Gy x rays at G_2											
AT19BI	1	50	1	0	1	13	6	3	0	0	0
AT5BI	11	50	26*	3	10	41	25	0	0	0	1
Con 1584		50	0	0	1	11	3	0	0	0	0
Con 1585		50	0	0	1	4	2	0	0	0	0
After exposure to 1·0 Gy x rays at G_2											
AT19BI	1	50	1	0	3	16	10	0	0	1	0
AT5BI	11	50	22*	1	9	84	53	0	0	5	2
Con 1584		50	0	0	3	9	5	0	0	2	1
Con 1585		50	0	0	1	8	6	1	0	0	0
After exposure to 4·0 Gy x rays at G_0											
AT19BI	1	50	26	64	127	3	2	0	1	4	1
AT5BI	11	50	60*	76	156	16	3	0	0	12	0
Con 1584		50	26	40	96	2	6	1	0	0	0
Con 1585		50	23	33	79	9	0	1	0	0	0

*High levels of rings in AT5BI are due to the presence of a ring containing clone (Taylor *et al*[17]).
tric=tricentrics; tri=triradials; qr=quadriradial chromosomes.

TABLE 3 *X ray induced chromosome damage at 48 hours after exposure to 1·0 Gy at G_2 (44 hours).*

Patient	*Sample No*	*No of cells*	*r*	*dic*	*f*	*ctg*	*ctb*	*csg*	*tric*	*tri*	*qr*
A-T 'variants'											
AT1AB	1	50	0	0	0	48	23	0	0	2	2
AT19BI	2	50	0	0	0	31	10	0	0	1	0
AT38BI	1	50	0	0	9	32	24	1	0	0	0
	2	50	0	0	3	19	4	0	0	0	0
	3	50	1	1	0	16	10	0	0	0	0
A-T 'classical'											
AT2BI		50	0	5	5	115	34	0	1	1	2
AT8BI		50	1	2	22	185	76	3	0	1	0
AT5BI	3	50	0	2	4	69	29	0	0	0	0
	12	50	40*	0	7	76	35	0	0	3	5
AT17BI		50	0	1	5	60	22	0	0	0	0
AT7BI		50	1	0	2	42	28	0	0	5	3
Normal controls											
Con 1230		50	1	0	1	6	7	0	0	0	0
Con 1446		50	0	0	1	9	2	0	0	0	0
Con 1657		50	1	0	1	6	4	1	0	0	0
Con 2107		50	0	0	0	17	3	0	0	0	0
Con 2112		50	0	0	0	18	2	0	0	0	0
Con 2146		50	0	0	0	20	2	0	0	0	0

*High levels of rings in AT5BI are due to the presence of a ring containing clone (Taylor *et al*[17]).

three times more radiosensitive than those from AT19BI. The number of aberrations produced in AT19BI after 0·5 Gy was very similar to the level in normal controls. There is clearly a considerable difference in radiosensitivity between the two patients by this criterion. The decreased radiosensitivity in AT19BI was confirmed in a second blood sample (table 3). Table 3 also shows results from samples from AT5BI taken both before and after those in table 2. Lymphocytes from AT1AB and AT38BI showed a lower than average increase in chromosomal radiosensitivity, although for AT1AB there is some overlap in radiosensitivity with AT7BI. The radiosensitivity of AT38BI was slightly less on average than that of AT19BI by this criterion (tables 2 and 3).

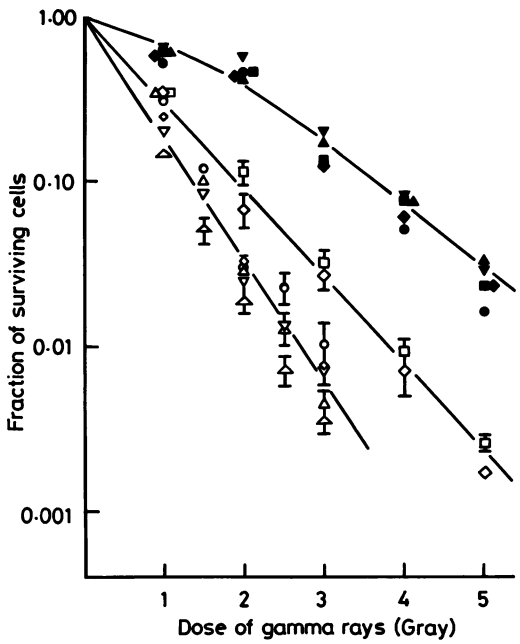

FIG 2 *Colony forming ability of normal and A-T fibroblast strains after exposure of cells to γ ray doses of 1 to 5 Gy. Mean D_0 values calculated by linear regression are given with standard errors. The number of determinations for each D_0 value is given in brackets. Con Bak ▼, D_0=1·171 Gy (two expts); Con Bri ▲, D_0=1·326±6·1 Gy (eight expts); Con Bro ■, D_0=1·190 Gy (two expts); Con Cra ◆, D_0=1·306 Gy (two expts); AT38BI ●, D_0=1·080±0·039 (three expts); AT1AB □, D_0=0·809±0·034 Gy (six expts); AT19BI ◇, D_0=0·756±0·02 Gy (four expts); AT2BI △, D_0=0·525±0·02 Gy (three expts); AT3BI ▽, D_0= 0·579±0·036 Gy (three expts); AT4BI ◇, D_0=0·601±0·029 Gy (three expts); AT5BI ○, D_0=0·581±0·03 Gy (five expts); AT7BI △, D_0=0·490±0·01 (three expts).*

After simultaneous exposure of AT19BI and AT5BI to 4·0 Gy *x* rays at G_0, the high level of chromatid type damage seen in A-T cells at G_0 was observed only in AT5BI (table 2). AT1AB also showed an increase in G_0 induced chromatid damage, although perhaps not to the same degree as seen in the other A-T patients (table 4). Lymphocytes from AT38BI did not show the increase in G_0 associated chromatid damage (table 4).

SURVIVAL OF CULTURED SKIN FIBROBLASTS AFTER γ IRRADIATION

The survival of fibroblasts following γ irradiation is shown in fig 2. The D_0 values of AT1AB and AT19BI (calculated by linear regression analysis) were 0·809±0·034 Gy and 0·756±0·015 Gy respectively. The range of D_0 values for the five other A-T fibroblast strains was 0·490 to 0·601 Gy. On average AT1AB and AT19BI had a D_0 value about one third as great again as the mean of the other A-T fibroblast strains. The mean D_0 of the five normal control fibroblast strains was 1·273 Gy. D_0 values for AT19BI and AT1AB were intermediate between the other A-T strains and the normal fibroblasts, although clearly more like the former. The D_0 value for AT38BI was 1·080±0·039 which is smaller than

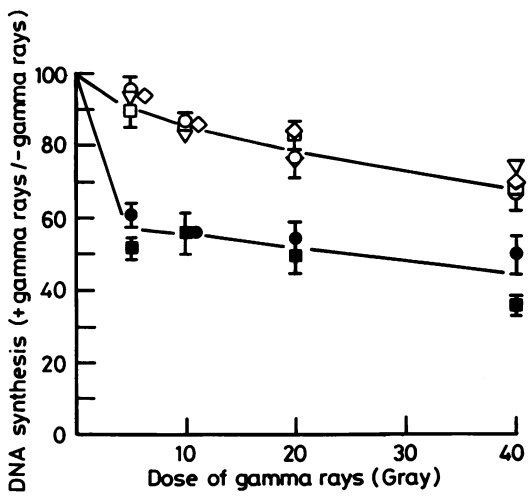

FIG 3 *The effect of increasing γ ray dose on DNA synthesis in normal and A-T fibroblast strains. Normals: Con Jon ● (three expts), Con Bro ■ (three expts). Classical A-T strains: AT3BI ▽ (two expts), AT5BI ○ (five expts). Variant A-T strains: AT1AB □ (six expts), AT19BI ◇ (three expts). Fibroblasts were prelabelled with [^{14}C] thymidine and either left untreated or irradiated. The cells were pulse labelled for 20 minutes with [^{3}H] thymidine and the number of counts in the acid insoluble fraction was determined. Ordinate $^{3}H/^{14}C$ ratio in γ ray exposed versus unexposed cells. Bars, SE.*

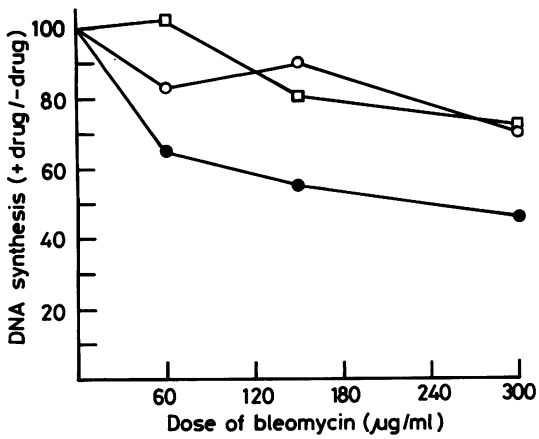

FIG 4 *The effect of increasing bleomycin dose on DNA synthesis in a normal, a classical A-T cell strain, and a variant A-T cell strain. Fibroblasts were prelabelled with [^{14}C] thymidine and were either left untreated or exposed for one hour to various concentrations of bleomycin (60 to 300 μg/ml). Cells were then pulse labelled for 20 minutes with [^{3}H] thymidine and the level of radioactivity in the acid insoluble fraction was determined. Ordinate, $^{3}H/^{14}C$ ratio in treated versus untreated cells. AT1AB (variant) □, (four expts), AT5BI (classical) ○ (four expts). ● The mean level of DNA synthesis in three normal fibroblast strains, Con Ree (two expts), Con Bak (one expt), Con How (one expt).*

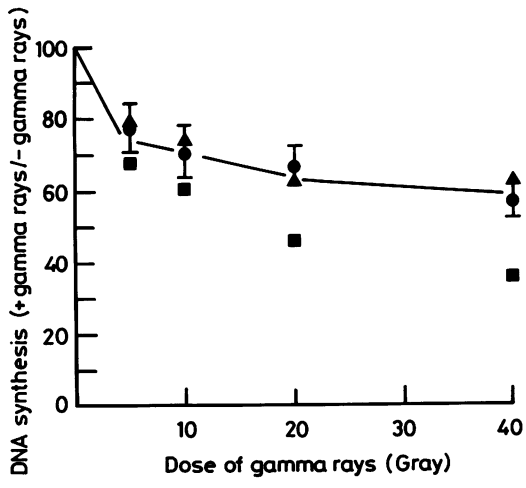

FIG 5 *The effect of increasing γ ray dose on DNA synthesis in normals Con How ■ (two expts), Con Bak ▲ (one expt), compared with a possible A-T variant AT38BI ● (three expts).*

the mean D_0 for normal cases, although there is some overlap with the normal range.

RESPONSE OF DNA SYNTHESIS AFTER EXPOSURE TO OTHER γ RAYS OR BLEOMYCIN

The rates of DNA synthesis in fibroblasts after exposure to γ rays (fig 3) show that in normal cases inhibition was much greater than in the A-T strains up to 40 Gy. No difference in the relative rates of DNA synthesis was observed between AT19BI and AT1AB and the other A-T strains. Both showed a marked lack of inhibition. The same pattern was observed after exposure to bleomycin with AT5BI and AT1AB, which showed the same lack of inhibition of DNA synthesis, the normal strains being inhibited to a much greater degree (fig 4). AT38BI showed a completely normal response of DNA synthesis following γ irradiation (fig 5).

Discussion

It has been suggested that within the group of patients diagnosed as having A-T there are different genetic entities. This has been shown by the presence of at least five different genetic complementation groups in cells from patients showing apparently the same degree of cellular radiosensitivity in vitro.[11 12] Whether or not these patients were clinically distinguishable one from another is unclear. We have described here clinical and cellular features of two patients in whom a clinical diagnosis of A-T was made, but where there were differences from other A-T patients.

Of the three variant patients, two showed a similar degree of spontaneous chromosome rearrangements as expected for A-T patients, but AT38BI did not. About 3% of AT1AB cells showed a t(7;14)(q35;q12) translocation which has been described previously in A-T patients.[5] AT19BI also showed spontaneous chromosome abnormalities including a t(6;15)(q23;q24) translocation. AT38BI showed the presence of a t(7;14) clone at a very low level.

The level of survival of cells from the two variants, AT19BI and AT1AB, is greater than that of classical A-T by about one third. D_0 values for the classical forms fell in the range 0·490 to 0·601 Gy, the same as the range reported by others.[4 18 19] The D_0 values for the two variants, 0·809 and 0·756 Gy, were very similar to values reported by Cox *et al*[9] for fibroblasts from two probable A-T patients and also by Taalman *et al*[14] for cells from a patient with a chromosome breakage disorder but without ataxia telangiectasia. The range of D_0 values for normal cases was again similar to other published results.[14 18 19]

Two principal chromosomal features of the unusual radiosensitivity in A-T are the high level of chromatid type aberrations observed after either G_0 or G_2 irradiation. Normal cells do not show any marked level of induced chromatid type aberrations following G_0 exposure. In AT1AB, and particularly in AT19BI, the level of G_0 induced chromatid aberrations was less than in lymphocytes from classical A-T patients (table 2). After G_2 irradiation, variant AT19BI showed very few induced chromatid type aberrations in two independent samples and the frequency in AT1AB was at the lower end of the range for classical A-T patients.

A comparison of fibroblast radiosensitivity measured by colony forming ability and lymphocyte chromosomal radiosensitivity can be made. The classical group of A-T patients in tables 3 and 4 may be tentatively ranked, particularly in table 3, by decreasing chromosomal radiosensitivity into three groups. Group 1 consists of sibs AT2BI and AT8BI. Although there is variation between them they are clearly more sensitive than the other patients' lymphocytes. Group 2 contains the unrelated patients AT5BI and AT17BI. Cells from these patients show the same degree of chromosomal radiosensitivity and are believed to be in the same complementation group,[12] different from AT2BI and AT8BI. The relative lack of chromosomal radiosensitivity in AT7BI would suggest a third grouping. Nothing is known about genetic complementation in this patient's cells.

Colony survival from these classical A-T patients is clearly much reduced after exposure to γ rays (D_0 range 0·490 to 0·601 Gy) compared with normals, correlating broadly with increased chromosomal radiosensitivity in the lymphocytes. Within this group, however, there appears to be no strong correlation of decreased chromosomal sensitivity with increased survival. Fibroblasts from patient AT7BI, for example, appear to be most sensitive (D_0=0·490 Gy) although chromosomally her lymphocytes were the least sensitive. Different factors may contribute to this apparent lack of correlation. Only a single fixation point of 48 hours was used for lymphocyte chromosome preparations. Irradiation at four hours before harvesting is unlikely to represent an identical stage in G_2 in all the cultures examined, and some differences may be due to this effect. There is a measurable difference in chromosomal radiosensitivity between sibs AT2BI and AT8BI, suggesting that perhaps cell cycle features may be important in the differences. Repeated samples from the same patient did, however, show broadly the same level of aberrations (for example, AT5BI, table 3). The comparison of survival and chromosomal sensitivity would be better made with fibroblasts alone.

It is notable, however, that lymphocytes from AT1AB and AT19BI both show low levels of radiation induced chromosome aberrations and higher survival, suggesting that there may be a general correlation of lymphocyte radiosensitivity and fibroblast survival.

There is clearly no sharp delineation between the level of radiosensitivity shown by the classical form of A-T and the variant form. Genuine differences in the degree of radiosensitivity between patients will be difficult to observe because of experimental error, the existence of a range of radiosensitivity for each group, and the rather restricted overall range in which these variations must exist.

The rate of DNA synthesis is inhibited to a much

TABLE 4 *X ray induced chromosome damage at 48 hours after exposure to 4·0 Gy at G_0.*

Patient	*Sample No*	*No of cells*	*r*	*dic*	*f*	*ctg*	*ctb*	*csg*	*tric*	*tri*	*qr*
A-T 'variants'											
AT1AB	1	50	23	108	207	11	5	0	7	4	1
AT38BI	1	50	5	47	78	2	0	0	0	0	0
A-T 'classical'											
AT2BI		50	25	62	215	36	17	2	4	11	2
AT8BI		50	26	46	327	44	17	4	1	12	0
AT5BI	3	50	34*	43	130	11	0	0	2	7	0
	7	50	59	56	167	12	7	0	1	1	2
AT17BI		25	25	24	81	8	3	0	3	6	1
AT7BI		50	39	39	124	18	10	7	0	19	4
Normal controls											
Con 1230		50	22	54	109	4	3	0	0	0	0
Con 1657		50	21	38	123	0	0	1	0	0	0
Con 1677		50	26	31	106	4	0	0	0	0	0
Con 1695		50	27	32	128	2	2	0	0	0	0

*High levels of rings in AT5BI are due to the presence of a ring containing clone (Taylor *et al*[17]).

TABLE 5 *Chromosomal and cellular features of different A-T patients.*

	Classical A-T	*AT19BI*	*AT1AB*	*AT38BI*
(1) Increased spontaneous stable and unstable chromosome aberrations	+++	+++	+++	+++
(2) Increased chromosomal radiosensitivity				
(a) Chromatid type damage at G_0	+++	+	++	Normal
(b) Chromatid type damage at G_2	+++	+	++	+
(3) Decrease in colony forming ability	+++	++	++	Normal
(4) High level of the rate of DNA synthesis	+++	+++	+++	Normal

greater extent in normal cells than in A-T cells after exposure to γ irradiation or to a range of chemical agents including bleomycin.[20–26] A good correlation between diminished DNA synthesis inhibition and enhanced cell killing in carcinogen treated A-T cells was suggested by Jaspers *et al.*[23] There is, however, a smaller degree of radiosensitivity in cells from AT1AB and AT19BI variants compared with the classical A-Ts, as measured by cell survival or chromosome breakage, but these two A-T variants produced the same rate of DNA synthesis as strains from classical patients after exposure to either γ rays or bleomycin. These two effects of radiation exposure (cell survival/chromosome aberrations and the rate of DNA synthesis) can therefore be expressed independently of each other in cells from patients AT1AB and AT19BI. A similar apparent anomaly has been reported for cells from a patient with unusual chromosome breakage but without A-T.[14] In this case an intermediate level of survival was associated with the same degree of inhibition of DNA synthesis as seen in cells from two A-T patients (AT3BI and AT5BI).

A more extreme example of the segregation of these two phenotypes has been reported by Lehmann *et al*,[27] who described an SV40 transformed cell line (derived from AT5BI), transfected with normal DNA, in which survival after irradiation was normal, but where the level of DNA synthesis after irradiation was similar to that in A-T cells.

Different genes may govern the responses of DNA synthesis and cell killing. The gene defective in A-T patients may be a controlling or regulatory gene affecting the expression of several other genes. Lehmann *et al*[27] suggest that in their cell line, suppression of the A-T radiosensitivity phenotype could have resulted from transfection or a second mutation. Patients AT1AB and AT19BI described here may be from one or more subgroups of A-T where the level of expression of all cellular phenotypes is not the same as in the classical form of the disorder. This differential expressivity might be due to further mutation within a pathway to a particular phenotype. More realistically in a recessive disorder, however, the differential expressivity may be due to modifying genes determined by the genetic background of a particular subject and this might also affect clinical expression of the disorder.

Some of the chromosomal and cellular features of A-T are given in table 5. Increased radiosensitivity in AT38BI, who is clinically not a typical A-T patient, is confined to a small increase in G_2 exposed lymphocytes. Other cellular features are normal. We believe, however, that the evidence from cytogenetics and colony survival experiments suggest that some A-T cells are clearly less radiosensitive than others. The cellular features shown by AT19BI and AT1AB fit well with the clinical diagnosis of ataxia telangiectasia. Cells from both patients undoubtedly show less chromosomal radiosensitivity and a greater fibroblast survival compared with the A-T patient cells.

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Variant forms of ataxia telangiectasia.

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